The evidence for immunotherapy in dermatomyositis and polymyositis: A systematic review.

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Abstract

Objectives: Dermatomyositis and Polymyositis are rare chronic inflammatory disorders with significant associated morbidity and mortality despite treatment. High-dose corticosteroids in addition to other interventions such as immunosuppressants, immunomodulators and, more recently, biologics, are commonly used in clinical practice, however there are no clear guidelines directing their use. Our objective was to systematically review the evidence for immunotherapy in the treatment of dermatomyositis and polymyositis.

Methods: Relevant studies were identified through Embase and PubMed database searches. Trials were selected using pre-determined selection criteria and then assessed for quality. Randomized controlled trials and experimental studies without true randomization and including adult patients with definite or probable dermatomyositis or polymyositis were evaluated. Any type of immunotherapy was considered. Clinical improvement, judged by assessment of muscle strength after 6 months, was the primary outcome. Secondary outcomes included IMACS definition of improvement, improvements in patient and physician global scores, physical function and muscle enzymes.

Results: Twelve studies met eligibility criteria. Differences in trial design, quality, and variable reporting of baseline characteristics and outcomes made direct comparison impossible. Although no treatment can be recommended on the basis of this review, improved outcomes were demonstrated with a number of agents including methotrexate, azathioprine, ciclosporin, rituximab and intravenous immunoglobulin. Plasmapheresis and leukapheresis were of no apparent benefit.

Conclusion: More high-quality randomized controlled trials are needed to establish the role of immunosuppressive agents in the treatment of these conditions and the clinical context in which they are most likely to be beneficial.

Introduction

Polymyositis and dermatomyositis are rare chronic inflammatory disorders of muscle, characterized by subacute onset of proximal muscle weakness, elevated muscle enzymes and inflammatory infiltrates on muscle biopsy. Characteristic cutaneous lesions are found in dermatomyositis. These conditions may occur in association with other autoimmune connective tissue diseases and there is significant overlap between the two diseases.

Treatment of inflammatory myopathies is generally empirical and subject to the experience of the treating physician. Despite having only recently been evaluated in the context of a randomized controlled clinical trial, glucocorticoids are the only FDA approved agents for treatment of these conditions and are generally accepted as being effective. As a substantial number of patients do not respond to glucocorticoids alone, additional agents such as immunosuppressants, immunomodulators, and, more recently, biologics, are commonly used in clinical practice. However, there are no evidence based guidelines to direct prescribing. Here we systematically review the evidence for immunotherapy in the treatment of dermatomyositis and polymyositis.

Materials and methods

Methods of analysis and eligibility criteria were specified in advance. The study conforms to the PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions.(1)

Search strategy

The search date was 4th February 2015. Potentially relevant citations were identified through Embase and PubMed database searches. The terms 'polymyositis', dermatomyositis', 'myositis' and 'idiopathic inflammatory myopathy' were combined and searched in conjunction with the following terms: corticosteroid, glucocorticoid, prednisolone, methotrexate, azathioprine, ciclosporin (cyclosporine A), cyclophosphamide, immunoglobulin, interferon, leflunomide, mycophenolate, plasma exchange, plasmapheresis, biologic, anti-tumour necrosis factor alpha, infliximab, etanercept, rituximab, and anakinra. Randomized controlled trial filters were used as described by the Cochrane collaboration.(2) Authors scrutinized the titles and abstracts to identify all relevant studies. Reference lists of relevant studies and related reviews were hand-searched to identify other potentially relevant citations.

Selection criteria

The following criteria were used to select studies for evaluation: the study was a randomized controlled trial or experimental study without true randomization (quasi-randomized study); the patients studied were adults (>18 years of age) with a diagnosis of definite or probable dermatomyositis or polymyositis according to either the Bohan and Peter(3, 4) or Dalakas (5) classification criteria; the study participants were judged to have active disease; and any type of immunotherapy was considered. The final inclusion and exclusion decisions were made after examining the full texts of all potentially relevant citations. Relevant data were extracted and analyzed and the results summarized in text and tables in three main

categories: study characteristics, baseline characteristics of study participants and outcomes. Trials were scored for quality using the Jadad scoring system.(6)

Outcome

The primary outcome was improvement in muscle strength, ideally after 6 months. Secondary outcomes included improvements in patient and physician global scores, physical function and muscle enzymes, and adverse events, in addition to achieving the International Myositis Assessment and Clinical Studies group (IMACS) Definition of Improvement (DOI) after at least 6 months. This combines a core set of six disease activity measures (physician global score, patient global score, muscle strength, physical function, muscle enzymes and extra-muscular involvement) and defines a clinically meaningful change for each.(7)

Statistical analysis

Results were analyzed using Review Manager 5.1 software (Cochrane Collaboration, Oxford, UK). The Cochran-Mantel-Haenszel chi-squared method was used to analyze dichotomous data and inverse variance was used for continuous data. Where possible, a Forest plot was created, using a random effects model, to display graphically the effect size and confidence interval of the effect. A *P*-value of <0.05 was considered statistically significant. As few studies were included in this review, and because there were significant differences in the study designs, populations, interventions and outcomes, meta-analysis and measurement of summary effects was not always possible.

Results

Search results

The preliminary search identified 2344 studies which were assessed for relevance. Thirteen were selected as potentially relevant, and one further relevant study was identified through hand-searching the reference lists of relevant studies. One previous systematic review on the topic was found.(8) Three studies were excluded after full assessment (one was an abstract with insufficient detail to fully assess against the selection criteria, one a follow-up study of an included trial and the other terminated early with only two participants reaching the primary endpoint). Eleven studies evaluating a total of 464 patients were included for further analysis. Figure 1 displays the flow of study selection and the characteristics of the included and excluded studies are summarized in Table 1.

Baseline characteristics

The baseline patient characteristics are summarized in Table 2. The average age across treatment groups ranged from 36 to 55 years, and the proportion of females ranged from 47 to 92%. Disease duration ranged from less than six months to more than five years, reflecting the inclusion of patients with refractory or relapsed myositis in a number of trials. Baseline muscle strength was reported in a number of ways. Most trials (9-16) used manual muscle testing (MMT) of various numbers of muscles or pairs of muscles, to give a summative score out of a total maximum. Vencovsky *et al*.(17) used a muscle endurance and function test (MEFT) with a maximum score of 56. Hollingworth *et al*.(18) used a composite score of muscle strength, muscle biopsy, electromyogram (EMG) and CK.

Responses

Table 3 summarizes the main outcomes of each study.

Improvements in muscle strength

Statistically significant improvements in muscle strength at 3 months were observed by Dalakas *et al.*(11) in the group receiving IVIg. However, this result was not reproduced by Miyasaka *et al.*(19) Although the group receiving IVIg showed numerically greater changes in MMT at 8 weeks than the placebo group, the differences were not statistically significant. Median time to improvement in muscle strength was shorter in the IVIg group, but this did not reach statistical significance.

Vencovsky *et al.(17)* (CsA and MTX group) demonstrated no significant difference between the CsA and MTX groups and, while significant improvements in muscle strength were demonstrated in all treatment groups by Ibrahim *et al.* (MTX, CsA and combination MTX/CsA), intention to treat analyses did not demonstrate any significant treatment effects. Hollingworth *et al.*(18) reported a non-significant trend towards benefit with ALG/AZA combination therapy compared to placebo, but incomplete outcome data reporting made calculation of effect size impossible. Villalba *et al.*(12) reported a non-significant trend towards benefit with combination MTX/AZA compared to IV MTX. Bunch *et al.* concluded that there was no benefit adding AZA to prednisolone at three months, (16) however, the long-term follow-up data showed a significant reduction in functional disability in the AZA group compared to the group given prednisolone alone.(20) Miller *et al.* reported no improvement in strength with either plasmapheresis or leukapheresis. (21) Oddis *et al.* demonstrated no significant difference in time to achieve a 20% improvement in MMT-8

between the early vs. late Rituximab groups.(9) Only 6 studies (9, 10, 12, 13, 15, 17) measured muscle strength at or after 6 months.

Physical function

Physical function was reported in seven studies. (11-15, 21) A number of measurement tools were used, including activities of daily living (ADL) score, based either on the modified Convery Assessment Scale (22) adapted for myositis or the Barthel Index,(23) the physical component of the Short Form 36 (SF-36),The Amyotrophic Lateral Sclerosis Functional rating Scale (24) and the Health Assessment Questionnaire (HAQ). A 9% significant improvement in functional rating scale was reported by Ibrahim *et al.* for all treatment groups (MTX, CsA and combination MTX/CsA) but these became non-significant in intention to treat analyses.(10) A non-significant trend towards benefit was noted by Villalba *et al.* in the group receiving combination MTX/AZA compared to IV MTX.(12) Dalakas *et al.* reported an improvement in ADL score from 65 (low) to 100 (normal) in the patients responding to IVIg, but no data were given for either the non-responders or placebo group,(11) and Miyasaka *et al.* reported numerically greater improvements in ADL scores in the IVIg group compared to placebo, but the difference was not statistically significant.(14) Numerically greater, although statistically insignificant, decreases in HAQ score were found in the patients receiving Etanercept compared to placebo(15) and van de Vlekkert *et al.* noted similar SF-36 scores in both the prednisolone and dexamethasone groups.(13) There was no evidence of improvement in patients receiving PEX or leukapheresis.(25)

Muscle enzymes

Muscle enzymes were reported in 8 studies.(10, 13-18, 25) No difference in CK was seen at 12 months in intention to treat analyses of MTX, CsA or combination MTX/CsA compared to glucocorticoids alone. There was no significant difference in the time to achieve normal muscle enzymes when comparing AZA and prednisolone to prednisolone alone at 3 months.(16) Long-term follow-up of these patients demonstrated a non-significant trend towards lower CK in the patients taking both prednisolone and AZA.(20) Hollingworth *et al.* reported a more marked improvement in CK in the group receiving IIS compared to the group receiving prednisolone alone.(18) When compared to baseline values, significant reductions in CK were noted in patients receiving PEX or leukapheresis but not sham apheresis,(21) and in patients given MTX or CsA in addition to prednisolone.(26) In the IVIg study where this outcome is reported, both placebo and treatment groups demonstrated significant reductions in CK when compared to baseline.(14) Similar improvements in CK were demonstrated in both prednisolone and dexamethasone groups (13) and Etanercept and placebo groups.(15)

Patient and physician global scores

Only two trials reported patient global scores as an outcome.(15, 17) Significant improvements were noted in patients receiving both MTX and CsA at 3 and 6 months when compared to baseline.(17) Similar improvements were noted in both Etanercept and placebo groups.(15) Only one trial reported physician global scores as an outcome: numerically greater improvements were noted in the Etanercept group when compared to placebo, but the difference was not statistically significant.(15)

IMACS Definition of Improvement

Only Oddis *et al* used this as an outcome measure. The use of Rituximab at weeks 0 and 1 in refractory patients failed to result in any significant improvement in time to DOI compared to Rituximab at weeks 8 and 9, or the proportion of patients achieving DOI at week 8 (end of placebo controlled phase). Despite this, 83% patients met DOI by the end of study evaluation and the mean prednisolone dose reduced significantly from baseline.(9) Changes in core set measures, including all those discussed above, were reported as being non-significant between the two intervention groups and data for each measure were not reported by the authors, however, they did report a reduction in mean/median scores over the follow-up period.(9) Later sub-analysis of this study showed that the presence of anti-synthetase or anti-Mi2 autoantibodies, juvenile onset disease and lower disease damage scores was highly predictive of achieving improvement following Rituximab.(27)

Safety and tolerability

Azathioprine Bunch *et al.* reported 2 withdrawals in the AZA group because of toxicity (intolerable GI side effects, pneumonitis).(16) None of the AZA-treated patients developed skin rash, oral ulceration, pulmonary disease, elevated liver enzymes, blood dyscrasias or renal abnormalities during the extended follow-up period.(20)

Villalba *et al.* reported a total of 11 withdrawals from the combination MTX/AZA treatment arm (6/15 during initial phase, 5/13 during crossover phase) for inefficacy or toxicity. Severe GI intolerance was the commonest cause of withdrawal (6 patients); there was 1 case of severe infection.(12) It is assumed that the remaining withdrawals were because of inefficacy. Overall, 36% of patients did not complete oral combination therapy. There was

no significant difference in the number of withdrawals when compared to the IV MTX group.(12)

Hollingworth *et al.* reported 14 withdrawals due to side effects. These were all fully reversible and known potential side effects.(18) Withdrawals were reported according to trial drug rather than subgroup, so these figures include patients with systemic lupus erythematosus, polyarteritis nodosa and myositis who were treated with the AZA/ALG combination.

Methotrexate Villalba *et al.* reported 11 withdrawals from the IV MTX treatment arm (7/15 during the initial phase, and 4/11 during the crossover phase). Four patients were withdrawn because of drug toxicity (GI intolerance, severe infection, rash, elevated liver enzymes) and 1 was withdrawn because of poor intravenous access.(12) It is assumed that the remaining 6 were withdrawn because of inefficacy. Overall, 61% of patients did not complete IV therapy. GI side effects were the commonest reason for discontinuation in the oral AZA/MTX arm (see under Azathioprine).(12) Lack of efficacy was noted in 16 patients receiving IV MTX and 8 patients receiving oral combination AZA/MTX.(12)
Vencovsky *et al.* reported 4 withdrawals from the oral MTX treatment arm due to toxicity (pancytopaenia, gut perforation, alveolitis, petechiae). None were withdrawn because of inefficacy.(17) Ibrahim *et al* reported 3 withdrawals from the MTX arm: 1 due to inefficacy, 1 due to toxicity, and 1 due to patient choice; 3 further patients were lost to follow-up. These 6 patients represent 50% of those enrolled in the MTX arm. In the same study, 3 patients

were withdrawn from the MTX/CSA arm: 2 due to toxicity and 1 to patient choice, with 1 further lost to follow-up, therefore only 74% completed combination therapy.(10)

Ciclosporin Vencovsky *et al.* reported 2 withdrawals because of toxicity (renal impairment, severe infection) and none for inefficacy. One patient was lost to follow-up.(17) Ibrahim *et al.* reported withdrawal in 1 patient because of toxicity and 3 due to patient choice, 1 other patient was lost to follow-up (31% enrolled).(10)

Rituximab Oddis *et al.* reported only one withdrawal due to an adverse event. Twenty-six serious adverse events were reported during the trial period, infections being the most common.(9) There were no differences in adverse events at week 8 (the randomized placebo controlled time point).(9) Predictably, infusion reactions were significantly more common in the Rituximab group compared to placebo: 2 events required hospitalization and 7 of 60 patients were not able to receive the full dose of Rituximab.(9) It is noteworthy that no glucocorticoids were administered at the time of study medication infusion, which may have influenced the incidence and seriousness of infusion reactions.

Plasma exchange and leukapheresis Miller *et al.* reported 1 withdrawal from the PEX arm due to deteriorating disease, and no improvement in 9 of the 13 treated patients. The condition of 3 of the 13 patients treated with leukapheresis deteriorated, and there was no change in the condition of 7. No patients were withdrawn from either arm because of toxicity, although the rate of adverse events in both arms was high.(21)

Intravenous immunoglobulin Dalakas *et al.* reported no withdrawals for inefficacy or toxicity in either the IVIg or placebo arm. IVIg was well tolerated, with the only reported adverse event being severe headache, which occurred in 2 patients and required treatment with opiate analgesics.(11) Miyasaka *et al.,* in contrast, reported adverse drug reactions in 42.3% of patients with two serious events in one patient (increased CK and muscle weakness) which they deemed probably related to IVIg.(14)

Anti-lymphocyte globulin Hollingworth *et al.* reported 5 withdrawals due to toxicity. Common side effects included drug fevers and rashes, but 75% completed the course of ALG.(18) Again, these figures include all patients given ALG/AZA combination therapy, rather than the myositis patients only. Withdrawals due to inefficacy were not reported.(18)

Discussion

There is a lack of good quality clinical trials assessing treatment approaches in patients with IIM. Many of the trials that do exist assess treatment response in patients with refractory disease, who have failed to respond to conventional therapy either with corticosteroids alone or with additional Immunosuppression. (9-12, 14, 16, 18, 21) This may have implications when trying to apply the results to treatment naïve patients at diagnosis. Furthermore, idiopathic inflammatory myositis is an umbrella term encompassing a heterogenous group of diseases that is far from clearly defined by the subgroups dermatomyositis and polymyositis. While many of the included studies failed to demonstrate statistically significant improvements, this may be because of differential treatment responses between myositis subsets, as demonstrated by sub-analysis of the

rituximab trial.(27) Only one other paper analyzed the distribution of myositis-specific and myositis-associated autoantibodies between the two treatment groups, but the impact of the presence of various autoantibodies on outcome and response to treatment was not assessed.(17) Future studies should take into account the association of certain myositis-specific autoantibodies and responsiveness to therapy.(28)

Plasmapheresis and leukapheresis were of no apparent benefit and resulted in improvement in muscle enzymes but no other parameters assessed. Although muscle enzymes are used as an outcome measure in treatment of these conditions, it must be remembered that enzyme levels alone are an inadequate measure of clinical response in myositis, and active inflammation, as demonstrated on muscle biopsy or MRI, can be demonstrated in the setting of normal muscle enzymes.

IVIg is the only agent that has been demonstrated to have statistically significant benefit compared to placebo when used in the treatment of refractory myositis.(11) Disappointingly, a subsequent placebo controlled trial of IVIg did not reproduce these findings; the authors cite potential steroid carry-over effects, possible steroid myopathy and a small study population as potential explanations.(14) Given the different study locations and that *Dalakas et al*. exclusively enrolled patients with dermatomyositis whereas *Miyasaka et al.* included both dermatomyositis and polymyositis patients, it is also possible that differential treatment responses of myositis subsets or patient ethnicity influenced study outcomes. It should also be noted that these two studies used different IVIg formulations and dosing regimens.(11, 14)

Whilst the placebo controlled trial of AZA did not show any significant evidence of benefit at 3 months, long-term follow-up data did suggest benefits and patients treated with AZA were stronger and required less steroid than the group treated with steroids alone.(16, 20) The impact of all agents must be considered in light of the well-known detrimental side effects of long-term glucocorticoid exposure. Although the *Oddis et al.* study did not meet its end point, this study did demonstrate a significant steroid sparing effect with a statistically significant fall in prednisolone dose from baseline to the end point of the trial.(9) In contrast, *Ibrahim et al.* demonstrated no difference at the end of their trial in mean daily prednisolone dose between the placebo group and the different treatment groups. (10)

While the earlier study comparing MTX to CsA demonstrated significant improvement in muscle strength and function in both patient groups (no treatment was superior to the other), (17) *Ibrahim et al*. demonstrated no difference in intention to treat analyses for MTX, CsA or combination MTX/CsA compared to placebo.(10) The later study had a high proportion of patients discontinue or lost to follow-up (26-50% in each arm) and 24% (14/58) withdrew due to adverse events, suggesting either that these medications are poorly tolerated by many patients or that any perceived benefit is outweighed by side-effects.
In other trials comparing the traditional immunosuppressants, MTX was found to be better tolerated than either AZA or CsA.(17, 29) The relatively low cost of oral MTX, its acceptable safety profile and familiarity with its use in other rheumatic diseases are further advantages. Based on the recent *Ibrahim et al*. study, continued use of these agents is called into question, however it may be that the appropriate context needs to be more clearly defined:

patients in the *Ibrahim et al*. study had active disease despite steroid therapy but when the same agents were used in newly diagnosed children with juvenile dermatomyositis the results clearly favoured combination treatment, and MTX had a better safety profile compared to CsA.(30) While the evidence for use of these agents remains limited, they continue to be widely prescribed for a variety of myositis presentations. (31)

This systematic review has a number of limitations, mainly related to the number, quality and design of the studies analyzed. There are very few published randomized controlled trials in dermatomyositis and polymyositis and most literature regarding treatment of these rare conditions is in the form of case series and expert opinion. Of the studies that were selected for review, there were significant differences in study design and quality. Various outcome measures were used and were not directly comparable, and follow-up periods ranged widely. Furthermore, although all study participants were judged to have 'active disease', disease duration and previous treatments varied greatly. In addition, there was significant diversity in the range of treatments studied, with some treatments not being commonly used in clinical practice, e.g. ALG and IV MTX. This is unlikely to change, as there are a vast number of unstudied or inadequately studied potential treatment modalities for these rare conditions, including not only the traditional immunosuppressants, but also an ever-expanding repertoire of biologic agents.

Despite the fact that myositis is a rare disease it is remarkable that so few articles were deemed suitable for sub-review. The deficiency of good quality therapeutic trials in polymyositis and dermatomyositis is underlined here, and evidence-based prescribing

recommendations are not yet possible for these rare and difficult diseases. Such a result emphasises the ongoing need for national, multicentre randomised controlled clinical trials, particularly in treatment naive cases.

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Conflicts of interest

The authors declare they have no conflicts of interest

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Figure 1. Study selection in the systematic review

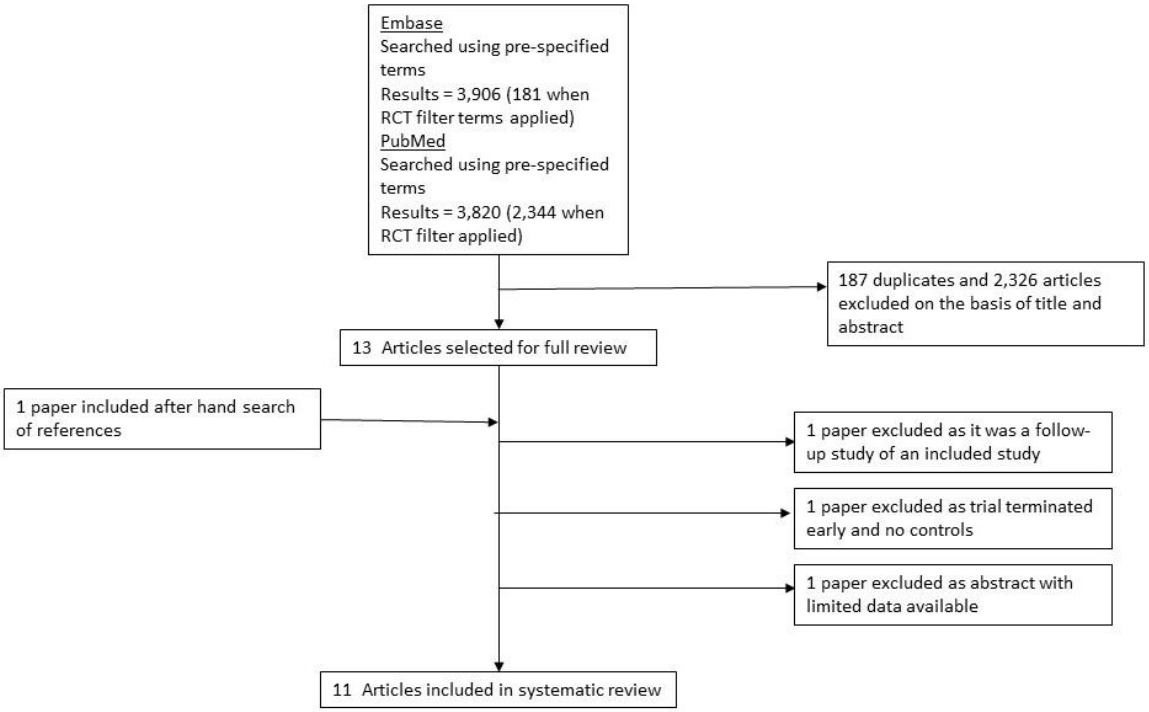

Table 1. A summary of studies short-listed for review

Short-listed studies are generally small, they assess a range of treatment options and use a variety of different outcome measures.

Study	**Year**	**Design**	**Cases**	**PM/DM/ Both**	**Intervention**	**Outcome**	**Follow-up**	**Jadad score**
Corticosteroids								
van de Vlekkert *et al.*	2010	Double-blind RCT	62	Both	Pred vs Dex	MMT15, CK, SF-36, neuromuscular symptom score, extramuscular features	18 months	5
Immunosuppressants								
Bunch *et al.*	1980	Double-blind RCT	16	PM	Pred + AZA vs Pred + PBO	MMT18, CK, muscle biopsy	3 months	3
Bunch *et al.* [a]	1981	Unblinded follow-up of RCT	16	PM	Pred + AZA vs Pred + PBO	Muscle strength, prednisolone dose, CK	1 & 3 years	2
Hollingworth *et*	1982	Randomize	14	Both	ALG + AZA + Pred	Composite score of strength,	2 years	2

al.		d open-label crossover			vs Pred	muscle biopsy, EMG, CK		
Miller *et al.* [a]	2002	Double-blind RCT	28	Both	Pred + AZA vs Pred + MTX	Myometry, functional assessment, VAS	1 year	2
Villalba *et al.*	1998	Randomized d open-label crossover	30	Both (Refractory)	Pred + MTX + AZA vs Pred + IV MTX	Strength/function score, MMT16, ADL score, CK	3 & 6 months	2
Vencovsky *et al.*	2000	RCT	36	Both	Pred + CsA vs Pred + MTX	MEFT, patient global, MRI, CK, serum IL-1Ra	1, 3 & 6 months	3
Ibrahim et al	2014	Double-blind placebo controlled RCT	58	Both	MTX, CsA, MTX + CsA, PBO	MMT, functional rating scale, 30m walk time, creatinine kinase, ESR	12, 28, 40, 56 weeks	5

Biologic agents								
Hengstman *et al.*[a]	2007	Open-label controlled trial	6	Both	Infliximab + MTX vs MTX	MMT8, dynamometry, patient global, physician global	6 months	1
The Muscle Study Group.	2011	Double-blind RCT	16	DM	Pred + ETAN vs Pred + PBO	MMT26, myometry, CK, disease activity, patient & physician global, physical function, cutaneous manifestations, quality of life	1 year	4
Oddis et al	2013	Double-blind placebo contolled RCT	200	Both & JDM (refractory)	Rituximab late or early	IMACS DOI, 20% improvement in MMT8	14 visits over 44 weeks	5
Other								

Dalakas *et al.*	1993	Double-blind RCT (crossover)	15	DM (Refractory)	IVIg vs PBO	MMT18, neuromuscular symptom score, ADL score, CK, muscle biopsy	3 & 6 months	5
Miyasaka *et al.*	2011	Double-blind RCT (crossover)	26	Both (Steroid-resistant)	IVIg vs PBO	MMT18, CK, ADL score	8, 16, 20 weeks	4
Miller *et al.*	1992	Double-blind RCT	39	Both	PEX vs Leukapheresis vs Sham apheresis	MMT, ADL score, CK	1 month	4

a. Excluded

ADL, activities of daily living; ALG, anti-lymphocyte globulin; AZA, azathioprine; CsA, Ciclosporin A; CK, Creatine Kinase; DM, dermatomyositis; Dex, dexamethasone; EMG, electromyogram; ETAN, etanercept; IL-1Ra, Interleukin 1 Receptor antagonist; IV, intravenous; IVIg, intravenous immunoglobulin; MEFT, muscle endurance and function test; MMT, manual muscle testing; MTX, methotrexate; PBO, placebo; PEX, plasma exchange; PM, polymyositis; Pred, prednisolone; RCT, randomized controlled trial

Table 2. Baseline characteristics of patients in the included studies

Study	**Cases, n**	**Age, mean**	**Female, %**	**Disease duration, months**	**CK, U//L**	**Muscle strength**
Corticosteroids						
van de Vlekkert et al. 2010	62 Pred: 32 Dex: 30	 Pred: 48 Dex: 49	65% Pred: 59% Dex: 67%	 Pred: 3.5 Dex: 4.5	 Pred: 4074 Dex: 2749	MMT15 (max 140) Pred: 128 Dex: 127
Immunosuppressants						
Bunch *et al.*1980	16 AZA: 8 PBO: 8	 AZA: 38.3 PBO: 40.9	69% AZA: 63% PBO: 75%	 AZA: 8.6 PBO: 9.6	 AZA: 2463 PBO: 809	MMT18 (max 90) AZA: -39.1 PBO: -27.1
Hollingworth *et al.* 1982	14	Pred: 50 ALG/AZA/Pred: 55 ALG/AZA/Pred	Pred: 50% ALG/AZA/Pred: 57%	Pred: 11 ALG/AZA/Pred: 14 ALG/AZA/Pred failure:	Data not shown	Data not shown

		failure: 42	ALG/AZA/Pred failure: 60%	40		
Villalba *et al.* 1998	30 MTX/AZA: 15 IV MTX: 15	 MTX/AZA: 41.5 IV MTX: 40.1	80% MTX/AZA: 80% IV MTX: 80%	 MTX/AZA: 45.1 IV MTX: 34.9	 MTX/AZA: 4023 U/l IV MTX: 2337 U/l	MMT16 (max 80) MTX/AZA: 58.1 IV MTX: 56.3
Vencovsky *et al.* 2000	36 MTX: 17 CsA: 19	 MTX: 38.4 CsA: 42.6	64% MTX: 82% CsA: 47%	 MTX: 30 CsA: 28	 MTX: 2535 CsA: 1629	MEFT (max 56) MTX: 24.1 CsA: 30.5
Ibrahim et al. 2014	58 MTX/CsA:15 MTX:12 CsA:16 PBO:15	 MTX/CsA:55 MTX:50 CsA:48 PBO:49	 MTX/CsA:73 MTX:83 CsA:63 PBO:60	 MTX/CsA:24.36 MTX:21.96 CsA:24.24 PBO:30.84	 MTX/CsA:310 MTX:104 CsA:326 PBO:309	MMT MTX/CsA:63 MTX:68 CsA:66 PBO:65
Biologic agents						
The Muscle Study Group.	16 ETAN: 11	 ETAN: 43.4	63% ETAN: 55%	 ETAN: 13.2	 ETAN: 821	MMT26 (max 13) ETAN: 4.5

2011	PBO: 5	PBO: 44.2	PBO: 80%	PBO: 26.4	PBO: 1098	PBO: 4.3
Oddis et al. 2013	152 Early RTX:73 Late RTX: 79	(includes JDM) Early RTX:43 Late RTX: 40	(includes JDM) Early RTX:71 Late RTX: 75	(includes JDM) Early RTX:62.4 Late RTX: 64.8	Similar in both groups but presented at times upper limit normal	(includes JDM) MMT-8 ratio Early RTX: 71 Late RTX: 71.7
Other						
Dalakas *et al.* 1993	15 IVIg: 8 PBO: 7	36	67%	IVIg: 46.8 PBO: 45.6	IVIg: 1076 U/l PBO: 842 U/l	MMT18 (max 90) IVIg: 76.6 (+/-59.7) PBO: 78.6 (+/-6.3)
Miyasaka *et al.* 2011	26 IVIg: 12 PBO: 14	IVIg: 50.6 PBO: 48.1	77% IVIg: 92% PBO: 64%	IVIg: 42% <6/12, 0% 6-12/12, 58% > 1 year PBO: 21% <6/12, 29% 6-12/12, 50% >1 year	Data not shown	MMT18 (max 90) IVIg: 61.8 PBO: 64.7
Miller *et al*. 1992	39 PEX: 13 Leukapheresis:	PEX: 41.5 Leukapheresis: 41.4	72% PEX: 69% Leukapheresis:	PEX: 37.2 Leukapheresis: 46.8 Sham: 28.8	Reported as similar, but data not shown	Reported as similar, but data not shown

	13 Sham: 13	Sham: 40.2	77% Sham: 69%			

ALG, anti-lymphocyte globulin; AZA, azathioprine; CsA, ciclosporin A; Dex, dexamethasone; IV, intravenous; IVIg, intravenous immunoglobulin; MEFT, muscle endurance and function test; MMT, manual muscle testing; MTX, methotrexate; PBO, placebo; PEX, plasma exchange; Pred, prednisolone; RTX, rituximab

Table 3. Summary of the main findings in each of the included studies

Studies analysed different immunosuppressive regimens and outcome measures. Most suggested a potential benefit from the addition of a second-line agent, although this was not always statistically significant.

Study	Muscle strength	Physical function	CK, U/L	Patient/ physician global	Withdrawals	Conclusion
Corticosteroids						
van de Vlekkert *et al.* 2010	MMT15 Pred: 135 (+7) Dex: 136 (+9)	SF-36 (physical component, max 100) Pred: 40 Dex: 39	Pred: 100 Dex: 197	NR	Pred: 17 withdrawals Dex: 21 withdrawals	Dex not superior to Pred, but causes less adverse effects
Immunosuppressants						
Bunch *et al.* 1980	MMT18 Pred + AZA: +6.5	NR	Mean days to normal CK	NR	PBO: 1 for inefficacy, 1 for unrelated reasons	No benefit in adding AZA to pred

	Pred + PBO: +1.1 NS		measured Pred + AZA: 69.4 Pred + PBO: 53.5 NS		AZA: 2 for toxicity (GI, pneumonitis)	
Bunch *et al.* 1981	Improvement in functional grade[a] Pred + AZA: -1.5[b] Pred + PBO: -0.5[b]	NR	Pred + AZA: 49.1 (2463) Pred + PBO: 73.8 (809)	NR	AZA: 2 temporarily stopped for toxicity (CMV, leukopenia)	AZA group stronger and required less pred
Hollingworth *et al.* 1982	Minimal improvement in IIS group	NR	More marked reduction in CK in IIS group	NR	NR	Trend toward additional benefit with IIS
Villalba *et al.* 1998	MMT NS trend towards	ADL score NS trend towards improvement in	NR	NR	MTX/AZA: 11 IV MTX: 11	Trend toward additional benefit with combination therapy

	improvement in MTX/AZA group	MTX/AZA group				
Vencovsky *et al.* 2000	MEFT Significant improvement in both groups^	NR	Significant decrease in both groups by 6 months[b]	Significant improvement in patient global^	NR	Addition of MTX or CsA confers benefit MTX cheaper, less toxic and better tolerated
Ibrahim et al. 2014	MMT Significant improvement but lost in intention to treat analysis	FRS Significant improvement but lost in intention to treat analysis	No difference in intervention groups on intention to treat analysis	NR	MTX/CsA:1 lost to follow-up, 2 toxicity, 1 other MTX: 3 lost to follow-up, 1 progression, 1 toxicity and 1 patient choice CsA: 1 lost to follow-up, 1 toxicity, 3 patient choice PBO: 2 lost to follow-up,	Improvements in disease activity measures but no difference in intention to treat analysis and therefore of questionable benefit.

					2 progression, 2 toxicity	
Biologic agents						
The Muscle Study Group 2011	MMT26 ETAN: 0.22 PBO: 0.27	HAQ ETAN: -0.44 PBO: -0.34	Log[CK] ETAN: -0.1 PBO: 0.16	ETAN: -1.7/-2.0 PBO: -2.1/-1.0	ETAN: 1 (lost to follow-up) PBO: 1 (lack of benefit)	No significant difference in outcomes, but ETAN appears safe and has a steroid-sparing effect
Oddis et al. 2013	MMT-8 Improvement but no significant improvement between RTX early or late groups	HAQ Improvement but no significant improvement between RTX early or late groups	Improvement but no significant improvement between RTX early or late groups	Improvement but no significant improvement between RTX early or late groups	5: 1 due to toxicity (late RTX group)	83% of patients met DOI but no significant differences between two treatment arms. Steroid sparing effect

Other						
Dalakas *et al.* 1993	MMT IVIg: +8.0[b] PBO: +0.0	ADL score Reported in responders only (+35)	NR	NR	NR	Benefit in refractory DM
Miyasaka *et al.* 2011	MMT18: IVIg: +11.8[b] PBO: +9.9[b]	ADL score (max 45) IVIg: +7.3 PBO: +4.0	Log[CK] IVIg: -1.16[b] PBO: -1.27[b]	NR	IVIg: 1 PBO: 0	Safe in steroid-resistant DM/PM, but no better than placebo
Miller *et al.* 1992	MMT No significant change in either group	ADL score No significant change in any group	Significant decrease in PEX and leukapheresis groups, not sham group	NR	NR	No benefit

a. Grades 1 through 6: 1 = normal to 6 = cannot walk

b. statistically significant $p<0.05$

ADL, activities of daily living; ALG, anti-lymphocyte globulin; ALT, alanine aminotransferase; AST,aAspartate aminotransferase; AZA, azathioprine; CsA, ciclosporin A; CK, creatine kinase; DOI, definition of improvement; DM, dermatomyositis; EMG, electromyogram; IIS, intensive immunosuppression (ALG + AZA + Pred); IV, intravenous; IVIg, intravenous immunoglobulin; LDH;, lactate dehydrogenase; MEFT, muscle endurance and function test; MMT, manual muscle testing; MTX, methotrexate; NR, not reported; NS, not significant; PBO, placebo; PEX, plasma exchange; PM, polymyositis; Pred, prednisolone; RTX, rituximab